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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,699	08/18/2003	Pascal Druzgala	04-1028-B	5094

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,699	DRUZGALA ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/18/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-29 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *23-29 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 07/18/2006, wherein claims 23, 24, and 34 have been amended.

The rejection of claims 23-29, 32, 33, and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is MAINTAINED. See under response to arguments.

Applicant's amendment is sufficient to overcome the rejection of claim 34 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is herein withdrawn.

Applicant's arguments have been considered, and found persuasive, the rejection of claims 23-25, and 32 under 35 U.S.C. 103(a) as being unpatentable over Kazuhisa et al. (JP 11035483, PTO-892) is withdrawn.

Applicant's arguments have been considered, and found persuasive, the rejection of claims 23-25, and 32-33 under 35 U.S.C. 103(a) as being unpatentable over Branca et al (US 4,808,605, PTO-892 of record) is withdrawn.

Claims 23-29, and 32-34 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-29, 32, 33, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement requirement, rejection of record**. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The instant claims are drawn to the method for blocking calcium channel in a patient in need of such treatment comprising administering to said patient a specific type of compounds having the structures shown in claims 23-29, and 34 (**Mibefradil analogs**).

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

The rejected claims are drawn to an invention, which pertains to a **method for blocking a calcium channel in a patient**, by the administration of a calcium channel blocking compound having the structures shown in claims 23-29, and 34.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a method of blocking a calcium channel by administering a compound having structures shown in claims 23-29, and 34. The breadth of the claims includes several compounds of structures shown in claims 23, 24 and 34.

(3). State of the Art / (4) Predictability of the Art:

The relative skill of those in the art is high.

The invention is directed to a method for blocking calcium channel by administering a compound having structures shown in claims 23-29, and 34. Applicants have **not provided any evidence or disclosed tests** for the pharmaceutical use for blocking calcium channel in a patient using the instant compounds. Pharmacological activity in general is highly unpredictable area. It is well established that the enablement varies inversely with the degree of unpredictability of the factors involved, and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839 (1970). The pharmacokinetic profile of a compound is governed by its physiochemical properties. More polar compounds will have low volume of distribution in more lipophilic tissues such as the heart and thus increase the

concentration in plasma. For example, the compounds represented with the structure as in claim 23, will have different physiochemical properties. The compound of structure in claim 23, with X = $(CH_2)_6$, and R_1 = C_6 alkyl will have different physical properties such as lipophilicity, binding abilities, hydrolyzability etc. than a compound with X = O, and R_1 = C_1 alkyl substituted with OH or NH2, and thus will have different calcium blocking ability or maybe lack any calcium blocking ability. In the instant case, the claimed invention is highly unpredictable because the claimed compounds represented by structures in claims 23-29, and 34 would not only have different calcium channel blocking ability or lack calcium channel blocking ability, but also different abilities towards enzymatic hydrolysis. Also, the enzymatic hydrolysis of the compounds represented by structures in claims 23, 24 calcium channel blockers results in metabolites with acidic functional groups. These acidic metabolites will have different distribution in plasma and lipohilic tissues. Thus, these novel mibefradil-based compounds and their metabolites of the instant invention have different functional groups and result in different biological properties such as drug-drug interactions, formation of metabolites with different toxicities etc. For example, mibefradil demonstrated efficacy in the treatment of hypertension and angina pectoris in man, but was withdrawn by the manufacturer due to drug-drug interactions based on the inhibition of cytochrome P-450. Thus, the instant claimed invention is highly unpredictable and **Applicant did not provide any factual evidence or testing results to show if these so-called analogs of mibefradil compounds can be used as calcium channel blockers**. Note that one of skill in the art would

recognize that instant compounds are Not considered to be analogs of mibefradil compounds, since their structures differ substantially.

(5). Guidance of the Specification / (6). Working Examples:

All of the guidance provided by the specification regarding calcium channel blocking compounds is directed to the following compounds: Verapamil, Diltiazem, Nifedipine, Mibefradil.

In the instant case, **no working examples or tests** are presented in the specification as filed to show if the instant compounds referred to as calcium channel blockers do indeed possess calcium channel blocking ability. Lack of a working example is a critical and crucial factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164. As discussed above, blocking a calcium channel in a patient in need of such treatment is highly unpredictable.

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of Mineral Separation v. Hyde, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of ordinary skill in the art would have to first envision a specific soft calcium channel blocking compound of the instant invention for the treatment, a dosage for each compound, the duration of treatment, route of treatment etc. One would then need to test the compound

in the model system to determine whether or not the compound is effective as a calcium channel blocker. One would then also need to test the compound in the model system for side effects and toxicity i.e magnitude of the change in the concentration of active species (parent drug and/ or active metabolite) at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in **undue experimentation** to test these novel mibefradil-based compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Response to Arguments

The rejection of claims 23-29, 32, 33, and 34 under 35 U.S.C. 112, first paragraph is MAINTAINED for reasons as discussed in the Non-Final Office Action dated 04/19/2006, and those found below.

Applicant argues that "One of ordinary skill in the art, comparing the structures of the compounds encompassed by the claims and that of mibefradil, would expect the compounds to have similar biological activity because they are stucturally similar." This argument has been considered, but not found

persuasive because compounds in claim 23, will have different physiochemical properties. The compound of structure in claim 23, with X = (CH2)6, and R1 = C6 alkyl will have different physical properties such as lipophilicity, binding abilities, hydrolyzability etc. when compared with mibefradil, and thus will have different calcium blocking ability or may lack any calcium blocking ability. For example, a compound with X = O, and R1 = C1 alkyl substituted with OH or NH2, R3 = (CH2)6-COOR6, results in a carbonate compound, which will have different physical properties such as lipophilicity, binding abilities, hydrolyzability etc. when compared with mibefradil (mibefradil has ester group, and R3 = CH3), and thus will have different calcium blocking ability or may lack any calcium blocking ability. In the instant case, the claimed invention is highly unpredictable because the claimed compounds represented by structures in claims would not only have different calcium channel blocking ability or lack calcium channel blocking ability, but also different abilities toward enzymatic hydrolysis.

Applicant's remarks that "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. Such is the situation here. The Applicants have taught how to make and use the invention, and the claims correspond in scope to the Applicants teaching. Further, the structural similarity between mibefradil and the compounds encompassed by the claims precludes any claim of doubt[ing] the objective truth" of the specification". These remarks have been considered, but not found persuasive because contrary to Applicant's assertion applicant has not

provided any data with respect to the method of using the claimed invention i.e the use of the instantly claimed compounds as calcium channel blockers. The correlation that Applicant is referring to is not reasonable because as discussed above the instant compounds of structure as in claim 23, have different functional groups as compared to mibefradil, and will have different physiochemical properties. Thus, in order to practice the claimed invention, one of ordinary skill in the art would have to first envision a specific soft calcium channel blocking compound of the instant invention for the treatment, a dosage for each compound, the duration of treatment, route of treatment etc. One would then need to test the compound in the model system to determine whether or not the compound is effective as a calcium channel blocker. Thus a person of skill in the art would have to engage in **undue experimentation** to test these mibefradil-based compounds encompassed in the instant claims with no assurance of success.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory

period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 7.30am-3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER